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Original Article

Impact of Therapeutic Interventions on Survival of Patients With Hepatic Hydrothorax

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Background/Purpose: Hepatic hydrothorax is an uncommon but important complication of liver cirrhosis. The optimal management of this condition remains unclear. This retrospective study evaluated the impact of therapeutic interventions on the outcome of patients with hepatic hydrothorax.

Methods: From August 1996 to March 2004, the medical charts of 52 patients with hepatic hydrothorax in the National Taiwan University Hospital were reviewed. Treatment methods, outcome of interventions, and survival time were described and analyzed.

Results: At the time of diagnosis, four patients were Child–Pugh class A, 20 were class B, and 28 were class C. Twenty-eight (53.8%) patients received supportive care with thoracentesis for symptom relief. Among the other 24 patients, 16 (30.8%) were treated by chemical pleurodesis, 14 (26.9%) underwent surgical interventions, and six (11.5%) received both interventions. Intervention success, defined as resolution of hydrothorax for at least 3 months after the procedure, was achieved in 37.5% and 42.9% of patients who underwent chemical pleurodesis and surgery, respectively, with an overall success rate of 50%. The median survival of all patients was 8.6 months (range, 0.2–77.6 months). The median survival of patients with intervention success (22.5 months) was significantly longer than those with intervention failure (5.4 months) and supportive care (6.3 months). Multivariate analysis showed that only intervention success ($p = 0.010$, hazard ratio = 0.25) was an independent predictor of survival.

Conclusion: For patients with hepatic hydrothorax, aggressive medical or surgical intervention might improve survival over supportive management, especially when resolution of hydrothorax can be maintained for at least 3 months.

Key Words: chemical pleurodesis, hepatic hydrothorax, surgery, survival

Hepatic hydrothorax is defined as significant pleural effusion, usually > 500 mL, in a patient with liver cirrhosis but no primary cardiac or pulmonary disease.[1–4] This is a relatively uncommon complication that occurs in approximately 5% of patients with cirrhosis.[4] In recent years, hepatic hydrothorax, along with hepatopulmonary syndrome and pulmonary hypertension, have been

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recognized as major pulmonary manifestations of chronic liver disease and cirrhosis.[5,6] Similar to refractory ascites, hepatic encephalopathy, or variceal hemorrhage, the presence of pleural effusion in patients with liver cirrhosis is usually indicative of advanced cirrhosis.[7]

The development of hepatic hydrothorax involves a complex pathophysiological process. The underlying mechanism for hepatic hydrothorax is unclear, although many mechanisms have been proposed, including hypoalbuminemia, azygos vein hypertension, leakage from the thoracic duct, transdiaphragmatic lymphatic migration, and pressure-gradient-directed flow through diaphragmatic defects.[4] There is accumulating evidence that diaphragmatic defects have a role in cases of hepatic hydrothorax in which blebs or fenestrations allow peritoneopleural communication.[8–10] Based on these findings, many reported treatments have been designed to eliminate the cause of hepatic hydrothorax.

Despite numerous case reports that have described clinical features and treatments, the optimal management of this condition remains unknown. Liver transplantation is the treatment of choice, but a donor is rarely available.[11] Other treatment options include repeated thoracentesis, pleurodesis,[12,13] placement of peritoneovenous shunts,[14,15] placement of a transjugular intrahepatic portosystemic shunt (TIPS),[16–18] and surgical repair of the diaphragmatic leak.[19] These are considered as temporary palliative measures only, and also as a useful bridge to transplantation.[11]

There are no guidelines on therapy of hepatic hydrothorax based on good evidence; therefore, most patients receive either supportive care or chemical pleurodesis for symptomatic relief. The optimal management, however, remains unclear and few previous studies have systematically evaluated the effect of therapy on clinical outcome in these patients. The aim of this study was to evaluate the impact of medical and surgical interventions on the outcome of hepatic hydrothorax at a tertiary hospital in Taiwan over an 8-year period. Our hypothesis was that aggressive medical or surgical interventions could improve the survival of patients with hepatic hydrothorax.

Materials and Methods

Patients and data collection

A retrospective study was conducted in adult patients with a confirmed diagnosis of hepatic hydrothorax who were admitted to the National Taiwan University Hospital, Taipei, Taiwan from January 1996 to March 2004. A total of 52 patients with complete medical records were included for analysis. In all patients, the diagnosis was liver cirrhosis, as indicated by clinical and laboratory findings, as well as by at least one imaging study (abdominal sonography, computed tomography, or magnetic resonance imaging). Chest radiography on diagnosis showed no cardiomegaly or active lung lesions except pleural effusion. All patients received therapeutic thoracentesis, and the results of cytology and microbial cultures of pleural effusion samples were all negative. All patients were put on a sodium-restricted diet, and diuretics and/or albumin were administered intermittently. Patients who underwent medical and/or surgical interventions were classified as the intervention group, and those who received supportive care with thoracentesis for symptomatic relief were classified as the supportive care group.

This research was approved by the Internal Review Board of the National Taiwan University Hospital.

Medical interventions

Medical interventions consisted of pleural drainage by chest tube thoracostomy followed by chemical pleurodesis with intrapleural introduction of sclerotic agents including minocycline, picibanil and beta-iodine.

Surgical interventions

Surgical approaches included thoracoscopic diaphragmatic repair by application of pleural flap and mesh onlay reinforcement, direct suture repair via video-assisted thoracoscopic surgery (VATS),

Denver shunt placement, and pleurodectomy. The details of the pleural flap and mesh onlay method have been previously reported.[20]

Supportive care

Patients in this group received intermittent thoracentesis for symptomatic relief only.

Outcome of interventions

Intervention success was defined as symptomatic relief and the absence of thoracentesis for a minimum of 3 months after the procedure. Patients who underwent medical or surgical interventions but did not meet the criteria of intervention success were considered as intervention failures.[21,22] The survival time was measured from the date of diagnosis of hepatic hydrothorax.

Statistical analysis

Values are expressed as mean ± standard deviation (continuous variables) or as a percentage of the group of origin (categorical variables). We used the Cox regression model to analyze the data. Censoring was defined for those patients who died during observation. For the outcome analysis, patients were categorized into intervention success, intervention failure and supportive care groups. We examined the association between intervention success and survival adjusted by potential confounders, including age, sex, Child–Pugh class, and presence of hepatocellular carcinoma (HCC). The potential confounders were selected on the basis of a demonstrated association with outcome of patients with cirrhosis in prior epidemiological studies.[23] All of these were retained in the model regardless of their statistical significance. The effects of clinical variables on survival are presented as relative risks with 95% confidence intervals. Only variables with complete data were analyzed in the study. Kaplan–Meier survival curves were constructed and the log-rank test was used to compare the intervention outcomes. All tests were two-sided and used a significance level of 0.05. The statistical analysis was performed using STATA statistical software version 8.0 (Stata Corp., College Station, TX, USA).

Results

The characteristics of the overall study population are shown in Table 1. At the time of diagnosis, four patients were diagnosed with Child–Pugh class A, 20 with class B, and 28 with class C. The etiology of liver cirrhosis was hepatitis B ($n=26$), hepatitis C ($n=17$), alcohol ($n=3$), primary biliary

Table 1. Characteristics of the study population*

Characteristic	All patients ($n=52$)	Interventions ($n=24$)	Supportive care ($n=28$)
Age (yr)	62.2 (12.6)	60.3 (11.6)	63.8 (13.4)
Sex, male:female	23:29	11:13	12:16
Child-Pugh class			
Class A	4 (7.7)	2 (8.3)	2 (7.1)
Class B	20 (38.5)	10 (41.7)	10 (35.7)
Class C	28 (53.8)	12 (50.0)	16 (57.1)
Etiology of liver cirrhosis			
HBV	26 (50.0)	11 (45.8)	15 (53.6)
HCV	17 (32.7)	9 (37.5)	8 (28.6)
Alcoholic	3 (5.8)	3 (12.5)	0 (0)
Miscellaneous	6 (11.5)	1 (4.2)	5 (17.9)
History of HCC	20 (38.5)	6 (25.0)	14 (50.0)
Death	41 (78.8)	16 (66.7)	25 (89.3)

**Data presented as n (%) or mean ± standard deviation. HBV = hepatitis B virus infection; HCV = hepatitis C virus infection; HCC = hepatocellular carcinoma.*

cirrhosis ($n=4$), autoimmune hepatitis ($n=1$), or cryptogenic ($n=1$). Hydrothorax was right-sided ($n=44$), left-sided ($n=6$), or bilateral ($n=2$). Six patients (11.5%) had isolated hepatic hydrothorax without demonstrable ascites. There was a higher incidence of HCC in patients who received supportive treatment only. Levels of protein and lactate dehydrogenase in the pleural fluids were 1.36 ± 0.84 g/dL and 150.2 ± 74.7 U/L, respectively. HCC was diagnosed in 38.5% of these patients.

Medical and surgical interventions

The intervention methods and clinical response of the intervention group are summarized in Table 2. Twenty-four patients underwent either chemical pleurodesis only ($n=10$), surgery only ($n=8$), or both ($n=6$). The sclerotic agents used for pleurodesis included minocycline only ($n=8$), picibanil only ($n=1$), minocycline + picibanil ($n=6$), or minocycline + picibanil + beta-iodine ($n=1$). For surgical interventions, the procedures included thoracoscopic diaphragmatic repair using pleural flap with mesh onlay reinforcement ($n=7$), direct suture repair via VATS ($n=3$), Denver shunt placement ($n=2$), and pleurodectomy ($n=2$). The success rates of chemical pleurodesis only, surgery only and both were 40%, 37.5% and 83.3%, respectively, with an overall response rate of 50%.

Outcome of interventions

Outcome was successful in six patients treated with chemical pleurodesis and in six treated with surgical intervention. Among the 12 patients with intervention failure, five were totally unresponsive to the intervention, three died within 3 months because of other cirrhosis-related complications, and four responded initially but suffered a recurrence of hepatic hydrothorax within 3 months after the intervention.

The mortality rate was higher in the supportive care group than in the intervention group during the observation period (89.3% *vs.* 66.7%, $p<0.05$). The median survival of all 52 patients was 8.6 months (range, 0.2–77.6 months). The survival of patients with intervention success was significantly longer ($p=0.002$) than those with intervention failure and supportive care (median survival = 22.5 months, 5.4 months, and 6.3 months, respectively) (Figure). In univariate analysis, presence of HCC ($p=0.024$) and intervention success ($p=0.002$) were significant predictors that affected survival. The multivariate analysis showed that only intervention success ($p=0.010$, hazard ratio = 0.25) was an independent predictor of survival benefit (Table 3).

Table 2. Treatment methods and response of the intervention population

Treatment	Response, *n* (%)	
	Success	Failure
Pleurodesis only ($n=10$)	4 (40.0)	6 (60.0)
Surgery only ($n=8$)	3 (37.5)	5 (62.5)
Both ($n=6$)	5 (83.3)	1 (16.7)
Total ($n=24$)	12 (50.0)	12 (50.0)

Discussion

This is believed to be the first study to examine the impact of therapeutic interventions on the survival of patients with hepatic hydrothorax. Our analysis after controlling for potential confounding variables suggests that successful intervention can improve survival in these patients.

Patients with hepatic hydrothorax have few therapeutic options, and standardized evidence-based treatment guidelines are lacking for patients

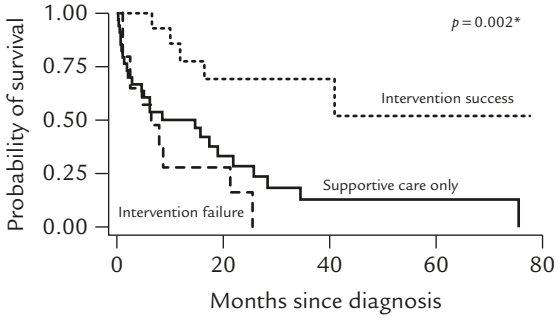

Figure. Kaplan–Meier survival curves of patients stratified by intervention strategies and outcomes. Patients who achieved intervention success had a higher rate of survival than those received supportive care only and those with intervention failure.

Table 3. Univariate and multivariate analyses of survival variable in intervention and supportive groups

Variable	Univariate analysis	Multivariate analysis	
	p	HR (95% CI)	*p*
Age	0.100	1.00 (0.97–1.02)	0.760
Child-Pugh class	0.290	1.25 (0.26–6.11)	0.780
Presence of HCC	0.024	1.17 (0.60–2.28)	0.650
Intervention success	0.002	0.25 (0.08–0.75)	0.010

HCC = Hepatocellular carcinoma; HR = hazard ratios; CI = confidence interval.

who fail to respond to diuretics. To the best of our knowledge, only one previous study has shown that aggressive intervention can have a survival benefit in these patients.[22] In that study, placement of a TIPS resulted in clinical improvements in 84% of patients with hepatic hydrothorax. All non-responders died within 7 months, whereas 70% of patients who responded to treatment survived for the first year of follow-up.[22] In our study, 50% of patients achieved intervention success and remained hydrothorax free. Patients with intervention success had better survival than those with intervention failure.

The increase in survival due to intervention success in our patients with hepatic hydrothorax could have resulted from the reduced risk of pulmonary or pleural infections. Cirrhotic patients with ascites are at risk for spontaneous bacterial peritonitis; likewise, patients with hepatic hydrothorax might acquire spontaneous bacterial empyema.[24] Xiol et al studied the clinical course of 120 cirrhosis patients with hydrothorax and reported that spontaneous bacterial empyema was present in 13% on admission, and was associated with a mortality rate as high as 20% during treatment.[25] Resolution of hydrothorax can eliminate a possible infection source in those immunocompromised patients. In addition, about one in four patients who underwent serial therapeutic thoracentesis subsequently developed pneumothorax.[26] Elimination of hydrothorax can therefore reduce potential complications that result from repeated therapeutic thoracentesis.

Medical treatment with salt restriction and diuretics is the mainstay of therapy for hepatic hydrothorax, but it only has a temporary effect in one-third of patients.[27] Several interventional strategies have been commonly used in the management of hepatic hydrothorax, including tube thoracostomy with chemical pleurodesis, repair of defects in the diaphragm, and the placement of a TIPS. Successful pleurodesis with tetracycline via tube thoracostomy for two patients with hepatic hydrothorax was first reported by Falchuk et al in 1977.[12] Lin et al also reported hepatic hydrothorax in two patients who were successfully treated with chemical pleurodesis with minocycline.[13] In our study, 16 patients received tube thoracostomy with chemical pleurodesis, and six (37.5%) were treated successfully. However, the rates of fluid re-accumulation were very high. Thoracoscopic or VATS pleurodesis might increase the success rate. Ferrante et al reported refractory hepatic hydrothorax in 15 patients who received VATS and talc pleurodesis, and 11 patients (73%) achieved resolution of effusion in the first 30 days after the procedure, with eight remaining asymptomatic for a median follow-up of 5.5 months.[28] Only three had recurrence between 45 and 60 days after the procedures. Cerfolio et al performed a retrospective review in 41 patients with refractory hepatic hydrothorax who underwent VATS with talc pleurodesis.[29] Overall success was achieved in 33 patients (80%) and only four experienced recurrence.

Moroux et al reported the use of VATS to repair diaphragmatic defects in addition to pleurodesis in eight patients with refractory hepatic hydrothorax.[30] The hydrothorax resolved in six patients (75%) treated with surgery. The mean follow-up time was 7–36 months and there was no recurrence of pleural effusion in any of the six patients who

responded. Milanez de Campos et al performed thoracentesis followed by talc poudrage under thoracoscopy and repair of diaphragmatic defects in 18 patients with persistent hepatic hydrothorax.[21] A total of 21 procedures were performed and the patients were followed for 3 months. Only 10 (47.6%) of the procedures were effective and there was recurrence in 43.7% of cases. In our study, 14 patients received surgical interventions, and six (42.9%) were successfully treated. There was a trend for a higher success rate among patients who underwent surgical intervention as compared with those who received chemical pleurodesis only (42.9% *vs.* 37.5%). Further randomized controlled trials, however, are required to confirm whether surgical interventions improve survival of patients with hepatic hydrothorax.

None of our patients underwent TIPS insertion for hepatic hydrothorax during the study period. Data in the literature on the effectiveness of TIPS placement in the management of refractory hepatic hydrothorax are impressive. This procedure can lead to symptomatic improvement in 70–80% of patients with refractory hydrothorax.[16,18,22] Although TIPS insertion is considered the procedure of choice for management of refractory variceal bleeding, its role in refractory ascites and hepatic hydrothorax awaits further prospective studies.[31] Nevertheless, encephalopathy and shunt occlusion are anticipated complications, which occurred in 25% and 31% of TIPS patients, respectively, in a large series.[32] According to Rossle et al, the TIPS procedure is probably one of the most difficult interventions in these patients and its results clearly depend on the skills of the operator.[33] There are also no reliable predictors for the success of this technique.[34] In our institution, experience with this technique has been disappointing, and surgeons are hesitant to perform this procedure in patients with hepatic hydrothorax. One of the authors (Dr P.M. Hwang) of the present paper has reported good results with pleural flap and mesh onlay reinforcement.[20]

Some limitations of our study need to be addressed. First, our intervention group was not homogeneous and was based on several interventional approaches (including agents used for pleurodesis, types of surgery, and sequence of interventions). It is therefore difficult to determine the optimal approach in these patients. Second, we failed to identify factors that were predictive of successful outcomes before therapeutic interventions. Although our study showed no survival benefit in the intervention failure group, many in this group reported improved quality of life and reduced severity of dyspnea. Perhaps this is because many of them had an initial response to the intervention and reduced pleural effusion before hydrothorax recurred. From this perspective, it seems reasonable to perform the intervention for all patients with hepatic hydrothorax if their condition permits. A further study with a prospective protocol may resolve these problems.

In summary, our results imply that aggressive medical or surgical interventions confer a survival advantage over supportive management in patients with hepatic hydrothorax, especially when resolution of hydrothorax lasts for a minimum of 3 months after the procedure. In addition, surgical interventions should be considered if hepatic hydrothorax is refractory to chemical pleurodesis.

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